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Mefv gene mutation frequency and clinical findings: A single center experience

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Abstract

Aim: Familial Mediterranean Fever (FMF) is a recurrent, self-limiting autosomal recessive disease. It is characterized by fever, peritonitis, pleuritis, arthritis, and erysipelas-like erythema. Mutations in the MEFV gene alter the structure of the pyrin protein, leading to the clinical manifestation of the disease. In our study, we aimed to evaluate the prevalence and clinical findings of MEFV gene mutations in the Marmara region

Material and Methods: Mutations in the MEFV gene were identified in 482 patients through DNA sequence analysis in a retrospective study.

Results: The most frequently detected mutation was the R202Q heterozygous mutation (135 patients, 25%). Other mutations were detected at the following frequencies: E148Q in 28% (135 patients), M680I in 2.48% (12 patients), R761H in 1.86% (9 patients), and M694V in 1.86% (9 patients). The most frequently detected homozygous mutation, however, was R202Q (22 patients, 4,56%).

Discussion: Here, we present the distribution of MEFV mutations and the frequency of clinical findings in 482 patients residing in Kocaeli province who were first diagnosed with FMF. The most frequently detected mutation in our study, R202Q, may be a contributing cause of the disease in FMF patients.

Keywords

Mefv Mutations, Fmf, R202q

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Introduction

Familial Mediterranean Fever (FMF) is a genetic disorder inherited in an autosomal recessive manner (OMIM:249100). It is caused by mutations in the MEFV gene (OMIM:608107) located on chromosome 16p13. The FMF is characterized by acute recurrent self-limiting episodes of fever, peritonitis, pleuritis, arthritis, and erysipelas-like erythema. Despite its prevalence in the Mediterranean region, FMF is also frequently observed among Turkish, Armenian, Arab, and Jewish communities. The Tel-Hashomer criteria, recommended by Livneh, are used for diagnosing FMF[1- 4].

FMF primarily manifests as abdominal pain; fever and arthritis are also frequent symptoms [5]. FMF may be misdiagnosed due to nonspecific clinical and laboratory manifestations; for example, sometimes it can mimic the symptoms of appendicitis. During FMF attacks, erythrocyte sedimentation rate (ESR), C-reactive protein, fibrinogen, and serum amyloid A (SAA) values often increase. Elevated SAA levels can lead to renal amyloidosis and chronic renal failure as long-term complications. Colchicine is used in treatment to prevent FMF attacks and to protect patients from long-term side effects [6]. To date, about 385 MEFV variants have been listed as mutations and polymorphisms in the Infevers database (https ://infevers.umai-montpellier.fr). Pathogenic mutations that cause FMF are generally located in exons 2, 3, 5, and 10. The most prevalent FMF-causing mutations identified in the population include M694V, M680I, V726A, M694I on exon 10, and E148Q on exon 2 [7, 8]. The MEFV gene exhibits other variants like A744S, R761H, I692del, E167D, and T267I. Additionally, there are five variants, namely K695R, E148Q, P369S, F479L, and I591T, which are classified as having unknown significance. The M694V mutation is the most common and pathogenic mutation in the Mediterranean region. Individuals with the M694V homozygous mutation exhibit symptoms that begin at an earlier age and are more severe. In addition, they are more prone to developing arthritis and amyloidosis [9, 10].

Due to the immigration from different parts of the country, the Marmara region has a diverse social structure. However, we believe that the number of FMF patients and their proportion within the population are high. In this study, we examined the MEFV gene mutation profile and its corresponding clinical findings.

Material and Methods

A retrospective analysis was conducted on 480 patients who presented to the Department of Medical Genetics at Kocaeli Derince Training and Research Hospital between 2016 and 2019 with a preliminary diagnosis of FMF. The MEFV gene mutation results and clinical findings of the patients were examined.

DNA isolation was performed according to the manufacturer's instructions (QIAamp DNA blood Maxi kit, Qiagen, Hilden, Germany). MEFV exons 2, 3, 5, and 10 were examined using DNA sequencing analysis . Separate PCR was performed for each exon, and nucleotide changes were detected using the Applied Biosystems 3500 Series (Thermo Fisher Scientific).

The study was conducted retrospectively, informed consent was not obtained from the participants.

Ethical Approval

This study was approved by the Ethics Committee of Kocaeli Derince Training and Research Hospital Ethical Board (Date: 2019-03-09, No: 2019/39).

Results

The study included a total of 482 patients, with 272 being female (56.4%) and 210 being male (43.6%), aged between 1 and 81 years. The mean age of patients was 24.41 ± 17.95 years. Of the 482 patients, 216 (44.8%) were in the pediatric group (<18 years) and 266 (55.2%) were in the adult group (≥18 years). The most common complaint in 70% of the study population was abdominal pain. Arthritis was reported as the second most common complaint, with a rate of 63.3%. The most common symptoms reported by the patients included fever in 50.8%, constipation in 29%, chest pain in 20%, gastroenteritis in 19%, erysipelas-like erythema in 9.5%, operated appendicitis in 8.5%, oral aphthosis in 8%, chronic renal failure (CRF) in 4%, pericarditis in 2%, and nausea in 1.2% .

MEFV mutation results detected in patients are classified in Table 1. Out of 482 patients, 6.19% (30 patients) were found to have a homozygous mutation, 46.5% (225 patients) had a heterozygous mutation, 29.5% (141 patients) had a compound heterozygous mutation, and 16.83% (82 patients) had a complex allele mutation.

The frequency of MEFV mutation is presented in Table 1,2

Table 1. Homozygous and Heterozygous Alleles

The MEFV mutation genotype distribution of patients	n	%
Homozygous alleles		
R202Q homozygous	22	4,56
V726A homozygous	4	0,82
M680I homozygous	2	0,41
M694V homozygous	1	0,2
E148Q homozygous	1	0,2
Total	30	6,19
Heterozygous alleles		
R202Q heterozygous	135	28
E148Q heterozygous	29	6,01
M680I heterozygous	12	2,48
R761H heterozygous	9	1,86
M694V heterozygous	9	1,86
V726A heterozygous	9	1,86
K695R heterozygous	7	1,45
V415V heterozygous	2	0,41
S339F heterozygous	2	0,41
C1245 heterozygous	2	0,41
P283R heterozygous	1	0,2
G304R heterozygous	1	0,2
E167D heterozygous	1	0,2
I506I heterozygous	1	0,2
M608I heterozygous	1	0,2
M694I heterozygous	1	0,2
E280K heterozygous	1	0,2
P706P heterozygous	1	0,2
C1010 heterozygous	1	0,2
Total	225	46,55

and 3. The most frequently detected mutation was the R202Q heterozygous mutation (135 patients, 25%). The frequencies of other detected mutations were as follows: E148Q in 28% (135 patients), M680I in 2.48% (12 patients), R761H in 1.86% (9 patients), and M694V in 1.86% (9 patients). However, the most frequently detected homozygous mutation was determined to be R202Q (22 patients, 4.56%). The frequencies of other homozygous mutations detected were as follows: V726A (4 patients, 4.56%), M680I (2 patients, 0.41%), M694V (1 patient, 0.2%), and E148Q (1 patient, 0.2%).

M694V/R202Q, the most common compound heterozygous allele, was observed in 19.29% of 93 patients. Other frequently detected compound heterozygous mutations were R202Q/V726A (8 patients, 1.65%), R202Q/E148Q (7 patients, 1.45%), V726A/M680I (5 patients, 1.03%), and P369S/R408Q (4 patients, 0.82%).

The most common complex allele is M694V heterozygous/R202Q homozygous, found in 2.68% (23 patients). Other identified complex alleles were M694V heterozygous/R202Q heterozygous/E148Q heterozygous (10 patients, 2.07%), M694V homozygous/R202Q homozygous (10 patients, 2.07%), M694V heterozygous/R202Q heterozygous/V726A heterozygous (9 patients, 1.86%), and M694V heterozygous/R202Q heterozygous/M680I heterozygous (8 patients, 1.65%).

Discussion

FMF is the most common autoinflammatory disease, clinically characterized by self-limiting inflammatory attacks. MEFV mutations primarily affect people in the Mediterranean region, particularly Arabs, Armenians, Turks, and Jews. According to the studies conducted in Turkey, the prevalence of FMF disease is 1:1000, and the carrier frequency is much higher, at a rate of 1:3 to 1:10. Studies have reported that FMF is commonly observed in the Turkish population worldwide [1- 3].

MEFV gene variant analyses are frequently used in daily practice to support clinical diagnosis. Around 20-30% of individuals with FMF have either no variant or only one variant in the MEFV gene [9, 11]. The most common mutations in Turkey are M694V, M680I, V726A, and E148Q, which are also prevalent among Arabs, Armenians, and Jews. The predominant mutations among Arabs are V726A, M680I, and M694V. While in Armenians, they are M694V, M680I, and V726A. In Egypt, the prevalent mutations are E148Q, M694I, and V726A. However, M694V and E148Q are more common among North African Jews, and E148Q, V726A are more common among Ashkenazi Jews [1, 2, 12, 13]. In a large study conducted on Turkish society, Dundar et al. identified 88 different variants in 27,504 patients; the most frequently detected variants were M694V (29.47%), E148Q (18.27%), R202Q (17.90%), M680I (10.61%), and V726A (10.14%) [8]. Bilge et al. reported in their study, which included 1,719 patients, that the most frequently detected variants were M694V (44.5%), M680I (12.3%), V726A (9.2%), and E148Q (1%) [14].

Table 2. Compound Heterozygous Alleles

Compound heterozygous alleles		
M694V heterozygous/R202Q heterozygous	93	19,29
R202Q heterozygous/V726A heterozygous	8	1,65
R202Q heterozygous/E148Q heterozygous	7	1,45
V726A heterozygous/ M680I heterozygous	5	1,03
P369S heterozygous/R408Q heterozygous	4	0,82
R202Q heterozygous/ R314H heterozygous	3	0,62
C329 heterozygous/C442 heterozygous	2	0,41
E148Q heterozygous/M608I heterozygous	1	0,2
R202Q heterozygous/A511E heterozygous	1	0,2
M694V heterozygous/R761H heterozygous	1	0,2
R202Q heterozygous/I259V heterozygous	1	0,2
E148Q heterozygous/P190P heterozygous	1	0,2
R202Q heterozygous/E225D heterozygous	1	0,2
M694V heterozygous/E148Q heterozygous	1	0,2
V726A heterozygous/F479L heterozygous	1	0,2
R202Q heterozygous/K695R heterozygous	1	0,2
R202Q heterozygous/M680I heterozygous	1	0,2
M680I heterozygous/R761H heterozygous	1	0,2
P706P heterozygous/M608I heterozygous	1	0,2
R202Q heterozygous/R652C heterozygous	1	0,2
V726A heterozygous/R761H heterozygous	1	0,2
R202Q heterozygous/ M680I heterozygous	1	0,2
E148V heterozygous/R151S heterozygous	1	0,2
R202Q heterozygous/R329H heterozygous	1	0,2
R202Q heterozygous/G304R heterozygous	1	0,2
R202Q heterozygous/R202G heterozygous	1	0,2
Total	141	29,07

Table 3. Complex Alleles

Complex alleles		
M694V heterozygous/ R202Q homozygous	13	2,69
M694V heterozygous/R202Q heterozygous/E148Q heterozygous	10	2,07
M694V homozygous/ R202Q homozygous	10	2,07
M694V heterozygous/R202Q heterozygous/V726A heterozygous	9	1,86
M694V heterozygous/R202Q heterozygous/M680I heterozygous	8	1,65
M694V heterozygous/R202Q heterozygous/R761H heterozygous	4	0,82
R202Q heterozygous/P369S heterozygous/R408Q heterozygous	4	0,82
M694V homozygous/R202Q heterozygous/R202G homozygous	4	0,82
E148Q homozygous/R151S homozygous	2	0,41
E148V heterozygous/P369S heterozygous/R408Q heterozygous	2	0,41
R202Q heterozygous/R202G homozygous	2	0,41
M694V heterozygous/R202Q heterozygous/A744S heterozygous	1	0,2
V726A heterozygous/ F479L heterozygous/E167D heterozygous	1	0,2
M694V homozygous/E148Q homozygous	1	0,2
R202Q heterozygous/E148Q heterozygous/L110P heterozygous	1	0,2
R2O2Q homozygous/C1245 heterozygous	1	0,2
M694V homozygous/R202Q homozygous/E148Q homozygous/M680 homozygous	1	0,2
M694V homozygous/ R202Q heterozygous	1	0,2
E148Q heterozygous/R151S heterozygous/I506I heterozygous	1	0,2
M694V heterozygous/R202Q heterozygous/C540C heterozygous	1	0,2
M694V heterozygous/R202Q heterozygous/M694I heterozygous	1	0,2
M694V heterozygous/R202Q homozygous/V726A heterozygous	1	0,2
M694V heterozygous/R202Q heterozygous/E230K heterozygous	1	0,2
M694V homozygous/V726A heterozygous/M680I heterozygous	1	0,2
A744S heterozygous/ R202G homozygous	1	0,2
Total	82	16,83
No mutation	4	0,82
Total	482	100

Nevertheless, in some studies, the frequency of detected variants varies significantly. In a study conducted on the Turkish population, Arpacı et al. reported that the most frequently observed variants in the analysis of 2,639 patients were R202Q (19.55%), E148Q (7.05%), M694V (6.51%), V726A (2.61%), and M680I (2%) [7]. In a study conducted by Celep et al., the most frequently detected variant was reported to be R202Q (50.1%) [16]. Similarly, in our study, the most frequently detected mutation was the R202Q heterozygous mutation (135 patients, 25%). However, the most frequently detected homozygous mutation was R202Q (22 patients, 4.56%).

The most common symptoms of FMF are abdominal pain, fever, arthritis, arthralgia, and erysipelas-like erythema. In their study involving 2838 FMF patients, Tunca et al. evaluated the clinical findings and reported that the most common clinical finding was abdominal pain [1]. In their investigation, Kalem et al. reported that the most prevalent symptom was abdominal pain, followed by fever [16]. In our study, the most common complaint in 70% of the patients was abdominal pain. Arthritis was the second most prevalent complaint, with a prevalence of 63.3%. Fever was observed in in 50.8% of our patients.

Conclusion

R202Q, which we still report as a polymorphism in our findings, is frequently detected in patients with FMF clinical symptoms. Similar to many other studies, the present study found that the R202Q variant was most frequently detected in patients diagnosed with FMF. To further understand the clinical impact of the R202Q variant, it must be evaluated in larger patient populations.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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